IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
Kevin P. BAKER, et al.	)	Art Unit: 1646
Application Serial No. 09/941,992	)	Confirmation No. 8312
Filed: August 28, 2001	)	Attorney's Docket No. 39780-2730 P1C1
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

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DATE MAILED: DECEMBER 12, 2005

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On September 16, 2004, the Examiner made a final rejection to pending Claims 124-126 and 129-131. A Notice of Appeal was filed on January 12, 2005, and Appellants' Appeal Brief was filed July 26, 2005.

An Examiner's Answer was mailed on October 12, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

Appellants have filed concurrently a Petition for Designation as New Grounds of Rejection Under 37 C.F.R. §1.181. A copy is enclosed herewith.

I. STATUS OF CLAIMS

The current application was filed with Claims 1-118. In a Preliminary Amendment filed on November 16, 2001, Appellants canceled Claims 1-118 and added new Claims 119-131. In an Amendment filed on October 24, 2003, Claims 119-123 and 128 were canceled and Claims 124 and 130 were amended. A Request for Continued Examination was filed July 7, 2004 in response to a Final Office Action dated January 21, 2004 wherein Claim 127 was canceled and Claims 124 -126 were further amended. A second final rejection was mailed September 16, 2004 and a Notice of Appeal was filed on January 12, 2005.

Claims 124-126 and 129-131 remain pending and under final rejection, wherein the final rejection of these claims is being appealed herein.

II. GROUNDS OF REJECTION

1. Whether Claims 124-126 and 129-131 satisfy the utility requirement under 35 U.S.C. §101.

2. Whether Claims 124-126 and 129-131 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

New references have been cited in the Examiner's answer.

III. ARGUMENTS

Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph

Concerning the rejection of Claims 124-126 and 129-131 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in her Answer, the Examiner argues that "the data do not support the implicit conclusion of the specification that PRO341 genomic DNA shows a positive correlation with lung cancer, much less that the levels of PRO341 polypeptides would be diagnostic as such." The Examiner cites the following arguments and cites new references in support of these conclusions:

Appellants disagree with each of the Examiner's arguments on a number for grounds.

1. New Grounds of Rejection have been made by the Examiner

First Appellants note that the Examiner has raised six new references for the first time in the Examiner's response. They are:

(1) Hittelman, 2001, Ann NY Acad. Sci 952:1-12;

(2) LaBaer; 2003, Nature Biotechnology 21:976-977;

(3) Chen *et al.*; 2002, Molecular and Cellular Proteomics 1:304-313;

(4) Gygi *et al.*; 1999, Mol. Cell. Biol. 19:1720-1730;

(5) Lian *et al.* 2001, Blood 98:513-524; and

(6) Fessler *et al*, 2002, J. Biol. Chem. 277:31291-31302.

These references were not previously cited in any of the prior rejections of record. Appellants submit that the citation of such new prior art references for the first time in an Examiner's answer constitutes a new ground of rejection and is not permissible.

The M.P.E.P. Section 1207.03 (III) states that:

> A new prior art reference cited for the first time in an Examiner's answer generally will constitute a new ground of rejection. If the citation of a new prior art reference is necessary to support a rejection, it must be included in the statement of rejection, which would be considered to introduce a new ground of rejection. Even if the prior art reference is cited to support the rejection in a minor capacity, it should be positively included in the statement of rejection. *In re Hoch*, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n. 3 (CCPA 1970). However, where a newly cited reference is added merely as evidence of the prior well known statement made by the examiner, the citation of the reference in the Examiner's answer would not constitute a new ground of rejection within the meaning of 37 C.F.R. §1.192(a)(2). See also M.P.E.P. §2144.03.

The M.P.E.P. adds that:

> In addition, if an Appellant has clearly set forth an argument in a previous reply during prosecution of the application and the Examiner has failed to address that argument, the Examiner would not be permitted to add a new ground of rejection

> in the Examiner's answer to respond to that argument but would be permitted to reopen prosecution, if appropriate. (Emphasis added; See M.P.E.P. §1207.03; Requirements for a new ground of rejection, II).

The Court of Customs and Patent Appeals considered this situation in *In re Hoch*, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n. 3 (CCPA 1970). In that case there were two other references cited in the appeal which were not mentioned in the statement of either of the appealed rejections. The court held:

> Appellant's complaint seems to be justified, and if we did not find the rejections based *solely* on Molotsky and the French patent to be sound, we might well feel constrained to reverse the decision of the board. Where a reference is relied on to support a rejection, whether or not in a "minor capacity" there would appear to be no excuse for not positively including the reference in the statement of rejection.

Appellants note that a Reply Brief must be in compliance with the requirements set forth in 37 C.F.R. §41.41. New or non-admitted affidavits and/or other evidence are not permitted in a Reply Brief.

For the detailed reasons set forth below, Appellants submit that the citation for the first time of these six references constitute new grounds of rejection and accordingly such rejections are not permissible.

Appellants have filed a Petition herewith which requests that the grounds of rejection and the six new references which are being cited in the Examiner's Answer in support of the grounds of rejection be designated new grounds of rejection. Appellants request a corrected Examiner's Answer which identifies the rejections as new grounds for rejection. Appellants request the prosecution be reopened.

2. The Examiner's arguments are improper.

The Examiner's arguments will be addressed in the order they are listed above.

(1) In making the rejection that "only three out of fourteen lung tumor samples tested positive" and "PRO341 was not amplified in any of the fourteen **colon** tumor samples" (emphasis added), the Examiner seems to indicate that a tumor marker is patentable only if the marker tests positive in a statistically high number of samples compared to the total number of samples tested

or if the tumor tests positive in every tissue type that was studied. However, this is not legally correct. Neither the M.P.E.P. nor the Utility Guidelines require that it is necessary for the Appellant to show a positive result in most or a larger percentage of the tissue samples studied in order to make an assertion of utility, nor are they needed to show that the tumor marker identifies cancers of various tissues types, *e.g.*: lung, colon, etc. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO341 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Furthermore, as indicated previously, it is well-accepted in the art that not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, even if the association of a tumor marker with a particular type of tumor lesion is rare, or, even if the occurrence of a particular kind of tumor lesion itself is rare, since such markers identifying rare tumors, they have great value in tumor diagnosis, and consequently, in tumor prognosis. The ΔCt values for PRO341 of at least 1.12-1.33 ΔCt units, which correspond to $2^{1.12}$ -$2^{1.33}$- fold amplification or

2.173 to 2.514 fold amplification in primary lung tumors, were considered significant according to the Goddard declaration. The skilled artisan would know the value and utility of rare tumor markers. Further, Appellants need not show that DNA was amplified in colon tumors as well for an assertion of utility.

(2) The discussions above under Point (1) also address the rejection that "very few ΔCt values were obtained that were at least 2".

(3) The Examiner says that "none of Livak *et al.*, Heid *et al.*, nor Pennica *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors" in rejecting the Goddard Declaration. Appellants strongly disagree. The above references were cited in the Goddard Declaration to show that quantitative TaqMan PCR assay is a well-known and widely used assay in the art for studying gene amplification in various cancers. For instance, the Goddard declaration clearly says that:

> "the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer."

Therefore, Dr. Goddard did not rely on the above mentioned references for determining whether "a 2-fold amplification is significant." The Examiner has misrepresented the actual purpose for presenting these references in the Goddard Declaration. Instead, the opinions expressed in the Goddard Declaration regarding the significance of the 2-fold amplification is based on Dr. Goddard's own scientific experience and factual findings. By making this rejection, the Examiner seems to disregard the expert's opinion based on her own personal disagreement over the significance or meaning of the facts offered, without solid support or scientific showing for her opinion(s). Appellants respectfully remind the Examiner that the Utility Examination

Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; **it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered**" (Emphasis added). Therefore, barring solid scientific evidence from the art that shows why a 2-fold amplification of DNA in the TaqMan PCR assay would not be considered significant by one skilled in the art, the basis for this utility rejection is flawed and is inappropriate.

(4) Regarding the Examiner's point on aneuploidy and the cited references, Sen *et al.* and Hittelman *et al.* **(newly cited)**, Appellants submit that both these references in fact, support the Appellants position regarding at least one utility for the PRO341 protein.

Appellants submit that even if the observed gene amplification for PRO341 were due to aneuploidy (which Appellants do not concede to), since aneuploidy itself is associated with early detection of cancer, the PRO341 gene would still be useful as a biomarker. This view is supported by the teachings of Sen and Hittelman. Appellants agree that while aneuploidy can be a feature of damaged tissue, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* support the Appellants' position. In other words, Sen supports the notion that aneuploidy may be used as a feature to identify either cancerous or pre-cancerous tissue or damaged tissue. For example, Sen *et al.* discloses in the abstract, "lines of evidence now make a compelling case for aneuploidy being a discrete chromosome mutation event that contributes to malignant transformation and progression process" (emphasis added; see page 82, line 4). Sen adds on page 83, "in colorectal tumors, chromosome aneuploidy is a common occurrence"; and further on page 84, line 5, "(i)n clinical settings, DNA ploidy measurements have revealed that DNA aneuploidy indicates high risk of developing severe premalignant changes in patients with ulcerative colitis, who are known to have an increased risk of developing colorectal cancer" and also on page 84, line 29 "in addition to being implicated in tumorigenesis and correlated with distinct tumor phenotypes, chromosome aneuploidy has been used as a marker of risk assessment and prognosis in several other cancers (emphasis added)."

Sen indicates throughout the article, several instances where aneuploidy is associated with many cancers, including, renal tumors, colorectal tumors, esophageal adenocarcinomas, papillary thyroid carcinomas, human breast cancer, cervical intraepithelial neoplasia, myeloid leukemia, etc. Therefore, in fact, according to Sen, even if the amplification observed for PRO232 were due to aneuploidy (which Appellants do not concede to), the PRO232 gene can at least be a marker for cancerous or pre-cancerous tissue or damaged tissue.

Appellants further submit that the art shows that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lesions. Appellants note the title of the Hittelman paper is "Genetic Instabilities in Epithelial Tissues at Risk for Cancer." Hittelman studied lung tissue from chronic smokers, which had been exposed for years to carcinogenic tobacco smoke. As Hittelman explains, "[t]umors of the aerodigestive tract have been proposed to reflect a 'field cancerization' process whereby the whole tissue is exposed to carcinogenic insult (*e.g.*, tobacco smoke) and is at increased risk for multistep tumor development (page 3). The detection of increases in chromosome number therefore identifies cells which have begun the first steps in this multistep progression to cancer. Even if these particular epithelial regions are not yet cancerous, their presence is strongly correlated with the development of cancer in the target tissue as a whole. Hittelman concludes that "**the measurement of chromosome instability in the target tissue will be useful in assessing cancer risk** as well as response to intervention" (page 10; emphasis added). Hittelman clearly teaches on page 2, fourth paragraph, line 3 that "it is important to identify individuals **at significantly increased cancer risk** who might best benefit from different types of intervention(emphasis added)." However, the Examiner states that a marker is useful for precancerous or damaged lung epithelium is not available in the Appellants' specification as filed. Appellants point out that, this point was well-established in the prior art, at the effective date of filing of this application, contrary to what the Examiner contends. Appellants submit that there was a shift towards detecting pre-malignant and early-malignant lesions of lung and associating aneuploidy, precancerous lung or damaged lung epithelium and early lung cancer detection in the prior art. For instance, it was known that lung

cancer was the end-stage of multi-step carcinogenesis, and in most cases, was driven by genetic and epigenetic damage caused by chronic exposure to tobacco carcinogens. It was also known that preneoplastic cells contained several molecular genetic abnormalities identical to those found in overt lung cancer cells, and well before the effective filing date of **July 9, 1998** of the present application, the therapeutic paradigm and focus had already shifted from targeting only clinically verified lung cancer toward targeting pre-malignant and early-malignant lesions. Furthermore, the prospects of lung cancer screening had become more meaningful as a consequence of developments in biology and radiology and better possibilities to define high risk populations most suitable for lung cancer screening. Articles in lung cancer and early-lung cancer detection published around and before July 9, 1998 collectively lent support to the view that it was important to detect, diagnosis and treat early lung cancer. Therefore, one skilled in the art of oncology, at the effective date of filing of the instant application, would have known, based on the teachings of the instant specification and the well-established art in lung cancer, how to make and use the instant PRO341 gene for the diagnosis of certain lung cancers, without undue experimentation.

(5) In support of the assertion that there is "a poor correlation between mRNA expression and protein abundance," the Examiner cited Pennica *et al.*, Konopka *et al.*, Hu *et al.* and new references by LaBaer *et al.*, Gygi *et al.*, Chen *et al.*, Lian *et al.* and Fessler *et al.*

References Pennica and Konopka were discussed previously in the Appeal Brief filed July 26, 2005 and Appellants maintain that they cannot be used to establish a poor correlation between mRNA and protein because these references did not show that, in general, it is more likely than not for mRNA and protein levels not to have a correlation. The reasons were clearly discussed in the Appeal brief.

Further, Appellants had also discussed the reasons why Hu *et al.* did not establish a *prima facie* case for lack of utility in their Appeal Brief. The Hu *et al.* reference entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added), drew conclusions based upon statistical analysis of information obtained from published literature, and

not from experimental data.

Similarly, the comments by LaBaer *et al.* entitled "Mining the literature and large datasets" is also based on statistical analysis like Hu, and offers an automated literature mining tool termed MedGene to comprehensively summarize gene-disease relationships. As was argued in the Hu reference, "some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes." Statistical analysis using literature mining is a very useful tool to assist the researcher in their analysis but may greatly overrepresent or underrepresent certain genes and thus their conclusions may not be generally applicable.

Appellants further submit that Gygi *et al.* too did not indicate that a correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). *Accurate prediction* is not a criteria that is necessary for meeting the utility standards. In fact, contrary to the Examiner's statement, similar to Haynes *et al.* (which was cited by the Examiner in the Office Action mailed January 21, 2004), the Gygi data also indicates **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies /cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell (emphasis added). Therefore, high levels of mRNA **generally** correlate with higher levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data, like Haynes *et al.*, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Appellants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

Nor is the analysis provided by Chen *et al.* applicable to the present application for the following reasons. First of all, Appellants note that the proteins selected for their study in Chen

et al. were identified by staining of 2D gels. As is well known, and was noted in Haynes *et al.* for instance, there are problems with selecting proteins detectable by 2D gels: "It is apparent that without prior enrichment only a relatively small and highly selected population of *long-lived, highly expressed proteins* is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus Chen *et al.*, by selecting proteins visualized by 2D gels, are likely to have excluded in their analysis many key regulatory proteins which could be candidate cancer markers.

Secondly, the manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Once again, Appellants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a

positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper which described gene expression of genes in adenocarcinomas and compared that to protein expression. In this paper they report that "these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression." The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma." Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

Accordingly, the data by Haynes, Gygi and Chen confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Appellants submit that the Examiner's Utility rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*, Gygi *et al.*, and Chen *et al.*

Regarding Lian *et al.*, Appellants submit that they only teach that protein expression may not correlate with mRNA level in differentiating myeloid cells and does not teach anything regarding such a lack of correlation for genes in general. In addition, the authors themselves admit that there are a number of problems with the data presented in this reference. At page 520 of this article, the authors explicitly express their concerns by stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and **proteins presented at low level will be missed**. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this **decreased the sensitivity of detection of minor proteins.**" (Emphasis added). It is known in the art that Coomassie dye stain is a very insensitive

method of measuring protein. This suggests that the authors relied on a very insensitive measurement of the proteins studied. The conclusions based on such measurements can hardly be accurate or generally applicable.

The Examiner also asserts that Fessler *et al.*, who examined lipopoysaccharide-activated neutrophilins, "found a 'poor concordance between mRNA transcript and protein expression changes' in human cells." Again, as with Lian *et al.*, Fessler *et al.* only examined the expression level of **a few proteins/RNAs** in response to LPS stimulation. Additionally, the PTO has overlooked a number of limitations of the study by Fessler *et al.* For example, as admitted by Fessler *et al.*, protein identification by two-dimensional PAGE limited to well-resolved regions of the gel, may perform less well with hydrophobic and high molecular weight proteins, and tends to select for more abundant protein species (page 31301, col. 1). Harvesting of the LPS-incubated PMNs at 4 hours may have prevented detection of earlier, **transient changes and may have thereby introduced artificial transcript-protein discordance**. Furthermore, the post-LPS incubation, pre-two-dimensional PAGE cell washes **would be expected to remove secreted proteins from further analysis**. In addition, because protein binding of Coomassie Blue has a limited dynamic range and is typically not linear throughout the range of detection, image analysis of Coomassie Blue-stained protein spots should only be consider as semi-quantitative (see page 31301, col. 1). Again, in this study, low abundance proteins were underrepresented. Appellants also note that the proteins in this study "removed secreted proteins from further analysis" while the proteins in the present application are secretory proteins. Therefore, Fessler's study cannot be applied to the present application.

In summary, both Fessler *et al.* and Lian *et al.* have relied on insensitive and inaccurate methods of measuring protein expression levels. The teachings of these two references cannot be relied upon to establish a *prima facie* showing of lack of utility.

For the reasons given above, Appellants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the new references cited in the Examiner's answer either and therefore, the Patent Office has failed to meet its initial burden of

For the reasons given above, Appellants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the new references cited in the Examiner's answer either and therefore, the Patent Office has failed to meet its initial burden of proof. Accordingly, this rejection under 35 U.S.C. §101 and §112, first paragraph, should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that the gene amplification assay disclosed in Example 170 of the specification, and the advanced state of the art in oncology, provide at least one patentable utility for the PRO341 polypeptides of Claims 124-126 and 129-131, and that one of ordinary skill in the art would understand how to use the claimed polypeptides and would have found such testing routine and not 'undue.' Therefore, Claims 124-126 and 129-131 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C1**).

Respectfully submitted,

Date: December 12, 2005

By: Leslie A. Mooi
Leslie A. Mooi (Reg. No. 37,047)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
Kevin P. BAKER, et al.	)	Art Unit: 1646
Application Serial No. 09/941,992	)	Confirmation No. 8312
Filed: August 28, 2001	)	Attorney's Docket No. 39780-2730 P1C1
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 35489**

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DATE MAILED: DECEMBER 12, 2005

PETITION FOR DESIGNATION AS NEW GROUNDS OF REJECTION UNDER 37 C.F.R. §1.181

MAIL STOP PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This Application is under Appeal. An Examiner's Answer was mailed on **October 12, 2005** in this case. This petition is filed:

☒ within two months of the mailing of the Examiner's Answer.

The proposed Reply Brief

☐ has been filed;
☒ is attached;
☒ with a request for Oral Hearing; and
☒ a Petition for designation of new grounds of rejection in the Examiner's Answer under 37 CFR §1.181

The application status is:

☐ Small Entity—fee $
☒ Large Entity—fee $
☐ Enclosed is Check No. _____ in the amount of $_____.
☒ The Commissioner is authorized to charge (or credit any overpayment) Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C1**) in the amount of **$130.00** for the Petition Fee.

STATEMENT

An Appellants' Appeal Brief was filed on July 26, 2005 and an Examiner's Answer was mailed on October 12, 2005 in this case. Concurrent with the filing of this Petition, Applicants are filing a Reply Brief and a request for an Oral Hearing.

Appellants submit that a number of grounds of rejection set forth in the Examiner's answer mailed on October 12, 2005 constitute new grounds of rejection. Appellants request that the grounds of rejection identified below and the six new references which are being cited in the Examiner's Answer in support of the grounds of rejection be designated new grounds of rejection. Appellants request a corrected Examiner's Answer which identifies the rejections as new grounds for rejection. Appellants further request that prosecution be reopened.

The Examiner has raised six new references for the first time in the Examiner's response. They are:

(1) Hittelman, 2001, Ann NY Acad. Sci 952:1-12;

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These references were not previously cited in any of the prior rejections of record. Appellants submit that the citation of such new prior art references for the first time in an Examiner's answer constitutes a new ground of rejection and is not permissible.

Legal Analysis

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The M.P.E.P. adds that:

> In addition, if an Appellant has clearly set forth an argument in a previous reply during prosecution of the application and the Examiner has failed to address that argument, the Examiner would not be permitted to add a new ground of rejection in the Examiner's answer to respond to that argument but would be permitted to reopen prosecution, if appropriate. (Emphasis added; See M.P.E.P. §1207.03; Requirements for a new ground of rejection, II).

The Court of Customs and Patent Appeals considered this situation in *In re Hoch*, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n. 3 (CCPA 1970). In that case there were two other references cited in the appeal which were not mentioned in the statement of either of the appealed rejections. The court held:

> Appellant's complaint seems to be justified, and if we did not find the rejections based *solely* on Molotsky and the French patent to be sound, we might well feel constrained to reverse the decision of the board. Where a reference is relied on to support a rejection, whether or not in a "minor capacity" there would appear to be no excuse for not positively including the reference in the statement of rejection.

Appellants note that a Reply Brief must be in compliance with the requirements set forth in 37 C.F.R. §41.41. New or non-admitted affidavits and/or other evidence are not permitted in a reply brief.

For the detailed reasons set forth below, Appellants submit that the citation for the first time of these six references constitute a new ground of rejection and accordingly such rejections are not permissible.

Detailed Analysis

(1) Hittelman, 2001, Ann NY Acad. Sci 952:1-12

The Examiner cites Hittelman for the first time on pages 5, line 17 - page 6, line 11, where the Examiner states:

> "the literature reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy *before* the epithelial cells turn cancerous. See Hittelman who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p.4, Figure 4. The gene amplification assay in the specification does not provide a direct comparison between the lung tumor samples and normal lung epithelium."

The Examiner cites Hittelman throughout the Examiner's Answer at, for example, page 14, lines 15-17; page 17, lines 8-15; page 25, lines 7-12; and page 31, lines 2-19.

The Examiner had not previously raised the issue of aneuploidy in damaged precancerous lung epithelium or the citation, Hittelman.

Appellants submit that they are unable to adequately rebut the Hittelman reference and each of the rejections based on Hittelman without presenting substantive evidence of their own. The M.P.E.P.

and the case law clearly state that the Examiner is not allowed to make new grounds of rejection and cite a new reference. Furthermore, it is inequitable to allow the Examiner to do so without allowing Appellants to present evidence in rebuttal. Appellants submit that the citation of Hittelman and raising of the grounds of rejection based on Hittelman constitute new grounds of rejection.

(2) LaBaer; 2003, Nature Biotechnology 21:976-977

The Examiner cites LaBaer for the first time on page 7, line 22 - page 8, line 4; where she states that:

> "One of the authors of this paper, Dr. LaBaer made an even stronger statement that reports of mRNA or protein changes of as little as two fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples."

The Examiner cites LaBaer throughout the Examiner's Answer, for example, in support of rejections at page 11, lines 6-7; page 12, lines 5-7; page 14, line 19 - page 15, line 2; page 18, line 18 - page 19, line 1; page 22, line 19 - page 23, line 1; page 25, lines 14 - page 26, line 7; page 27, lines 13-19, page 28, lines 14-18; page 29, lines 16-19; page 39, lines 18-21; page 44, lines 15-22; page 48, lines 11-19; and page 51, lines 11-19.

In this case, the Examiner's basis for rejection that differences of as little as two fold are not uncommon and that changes of this magnitude relate to disease-independent differences between the samples" is being made for the first time.

Appellants submit that they are unable to adequately rebut the LaBaer reference and each of the rejections based on LaBaer without presenting substantive evidence of their own. The M.P.E..P. and the case law clearly state that the Examiner is not allowed to make new grounds of rejection and cite a new reference, LaBaer. Furthermore, it is inequitable to allow the Examiner to do so without allowing Appellants to present evidence in rebuttal. Appellants submit that the citation of LaBaer and raising of the grounds of rejection based on LaBaer constitute new grounds of rejection.

(3) Chen *et al.*; 2002, Molecular and Cellular Proteomics 1:304-313

The Examiner states at page 7, lines 6-14 of the Examiner's response that "Chen *et al.*, (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung carcinomas. Only 17% of 165 protein spots or 21% of genes had significant correlation between protein and mRNA expression levels. Chen *et al.* clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products."

The Examiner makes reference to specific experimental details and statistical percentages present in the Chen reference for the first time. This constitutes a new ground of rejection.

The Examiner cites Chen throughout the Examiner's Answer, for example, in support of rejections at page 11, lines 4-10; page 12, lines 5-7; page 14, line 19 - page 15, line 2; page 16, lines 1-4; page 18, lines 2-10; page 22, lines 15-22; page 25, lines 14-20; page 27, lines 13-19; page 28, lines 10-14; page 29, lines 17-19; page 39, lines 18-20; page 41, line 16 - page 42, line 6; page 44, lines 13-15, page 48, lines 11-14 and page 51, lines 11-14.

Appellants submit that they are unable to adequately rebut the Chen reference and each of the rejections based on Chen without presenting substantive evidence of their own. The M.P.E.P. and the case law clearly state that the Examiner is not allowed to make new grounds of rejection and cite a new reference, Chen. Furthermore, it is inequitable to allow the Examiner to do so without allowing Appellants to present evidence in rebuttal. Appellants submit that the citation of Chen and raising of the grounds of rejection based on Chen constitute new grounds of rejection.

(4) Gygi *et al.*; 1999, Mol. Cell. Biol. 19:1720-1730;

(5) Lian *et al.* 2001, Blood 98:513-524; and

(6) Fessler *et al*, 2002, J. Biol. Chem. 277:31291-31302

Similarly, regarding (4) Gygi, (5) Lian and (6) Fessler, the Examiner cites these references for the first time in the Examiner's Answer on pages 8 through 9. The Examiner states that "Gygi conducted a similar study with over 150 polypeptides," "Lian show a similar lack of correlation in mammalian (mouse cells)," and "Fessler found poor concordance between mRNA transcript and protein expression changes in human cells." These references are presented for the first time and hence, constitutes a new ground of rejection.

These references are further cited throughout the Examiner's Answer in support of various rejections at, for example, page 11, lines 4-10; page 12, lines 5-7; page 14, line 19 - page 15, line 2; page 16, lines 1-4; page 19, line 8 - page 20, line 1, including a quote from Gygi; page 22, line 20 - page 23, line 1; page 25, lines 14-20; page 27, lines 13-19; page 28, lines 14-18; page 29, lines 17-19; page 39, lines 18-20; page 44, lines 13-15, page 48, lines 11-14 and page 51, lines 11-14.

Appellants submit that they are unable to adequately rebut these references and each of the rejections based on these references without presenting substantive evidence of their own. The M.P.E.P. and the case law clearly state that the Examiner is not allowed to make new grounds of rejection and cite a new reference. Furthermore, it is inequitable to allow the Examiner to do so without allowing Appellants to present evidence in rebuttal. Appellants submit that the citation of these references and

raising of the grounds of rejection based on these references constitute new grounds of rejection. Appellants further request that prosecution be reopened.

Appellants submit that this issue of the new grounds of rejections is being timely raised by the filing of this petition under 37 C.F.R. §1.181 with necessary fees and concurrently, with the filing of a Reply Brief within the two month period set for the Appellants' response.

Respectfully submitted,

Date: December 12, 2005

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